Bacteriophage T4

Editors: Christopher K. Mathews, Elizabeth M. Kutter, Gisela Mosig, Peter B. Berget

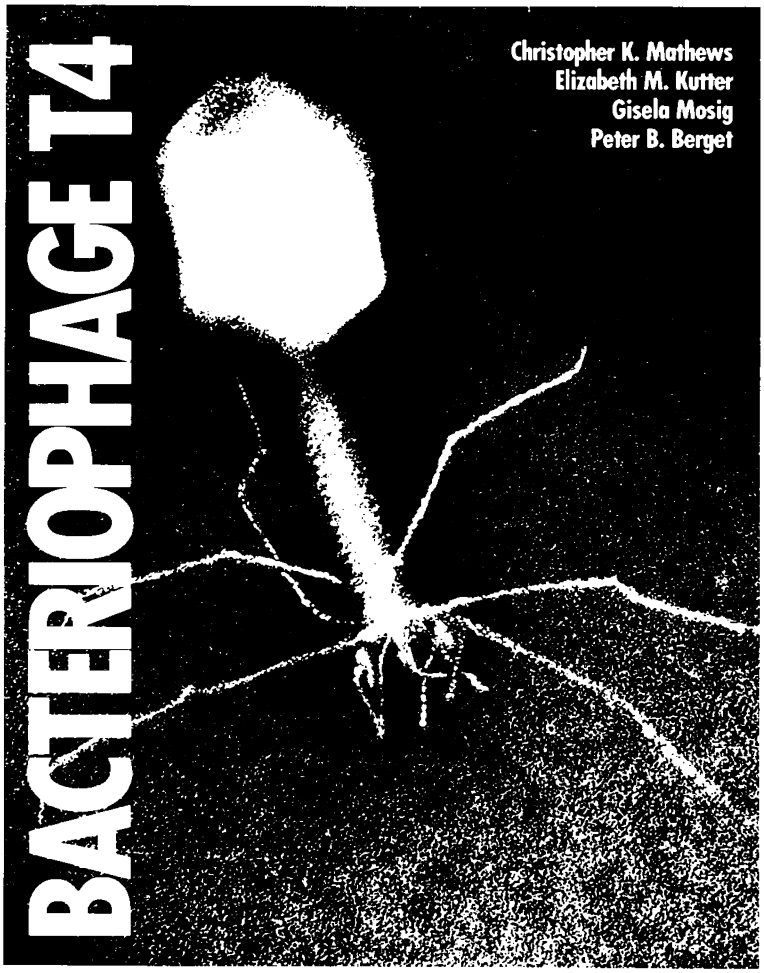
The outcome of the Evergreen T4 Meetings, this book presents a complete overview of T4 research, from its earliest history to its latest developments. T4 is a remarkable organism, one that has played an important part in the growth of molecular biology research. Here its story is told for the first time in one place. From Doermann's *Introduction to the Early Years of Bacteriophage T4* to Guttman and Kutter's *Overview* to Mathews' *Postscript,* this book is informative, comprehensive, and up-to-date.

The book will be useful for upper-level students, virologists, and molecular biologists—in fact, indispensable for anyone with an interest in bacteriophage T4.

The papers are arranged in the following sections:

I. T4 Structure and Initiation of Infection
II. DNA Metabolism
  A. Enzymes and Proteins of DNA Metabolism
  B. DNA Metabolism In Vivo
III. Regulation of Gene Expression
  A. Transcription
  B. Processing and Translation
IV. Morphogenesis
V. Structure, Organization, and Manipulation of the Genome
VI. Some Complexities of T4 Genes, Gene Products, and Gene Product Interactions

An appendix presents a table of T4 genes and gene products.



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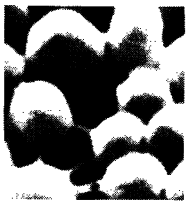

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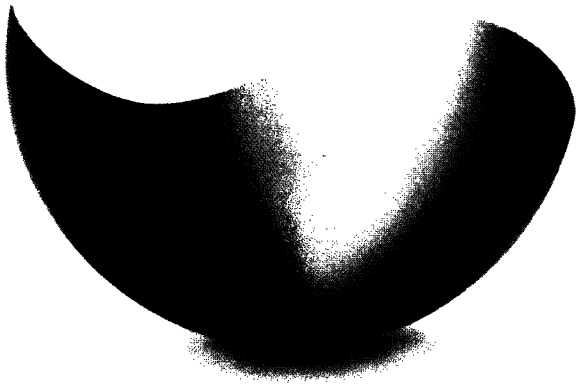

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in urinary tract infections
due to susceptible strains of Escherichia coli, Klebsiella and Enterobacter species

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COACTIN® IM IV
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500-mg and 1-gm vials

A new penicillin targeted for success

Targeted activity through PBP-2 binding
Unlike other beta-lactams that bind at penicillin-binding protein 1 or 3, COACTIN binds specifically to penicillin-binding protein 2 (PBP-2), achieving a unique morphological effect (ovoid formation). Since the PBP-2 binding sites are relatively few in number, COACTIN is able to more completely saturate its binding sites.

Besides its preferential PBP-2 binding, COACTIN (amdinocillin) has other notable features: It resists inactivation by beta-lactamases and there have been no reports of induced beta-lactamases.

In vitro: *Although a useful guide, in vitro activity does not necessarily correlate with clinical results.*

Highly active against the following gram-negative bacteria:

ORGANISMS	*NO. OF STRAINS TESTED*	*% OF STRAINS INHIBITED (4 µg/ml breakpoint)* 0 10 20 30 40 50 60 70 80 90 100
E. coli	2294	
E. coli (ampicillin resistant)	58	
Klebsiella pneumoniae	1011	
Enterobacter spp.	728	
Serratia spp.	360	
Citrobacter spp.	198	

Clinically:

Effective alone in complicated and uncomplicated urinary tract infections (UTI) due to susceptible organisms

Bacteriologic Cure*

Organism	*No. of Organisms*	*Eradicated No. (%)*
E. coli	163	162 (99.4)
Klebsiella	32	30 (93.8)
Enterobacter	7	7 (100.0)
Totals	**202**	**199 (98.5)**

*Data on file, Hoffmann-La Roche Inc.

Exhibits typical penicillin safety and toxicity.
The incidence of adverse reactions reported during clinical trials was low. Those reactions that occur are mild and comparable to those observed with other penicillins. As with any penicillin, there exists the possibility of hypersensitivity reactions, especially in individuals with a history of sensitivity.

During its investigative phase, amdinocillin was known as mecillinam.

Please see last page of this advertisement for complete product information.

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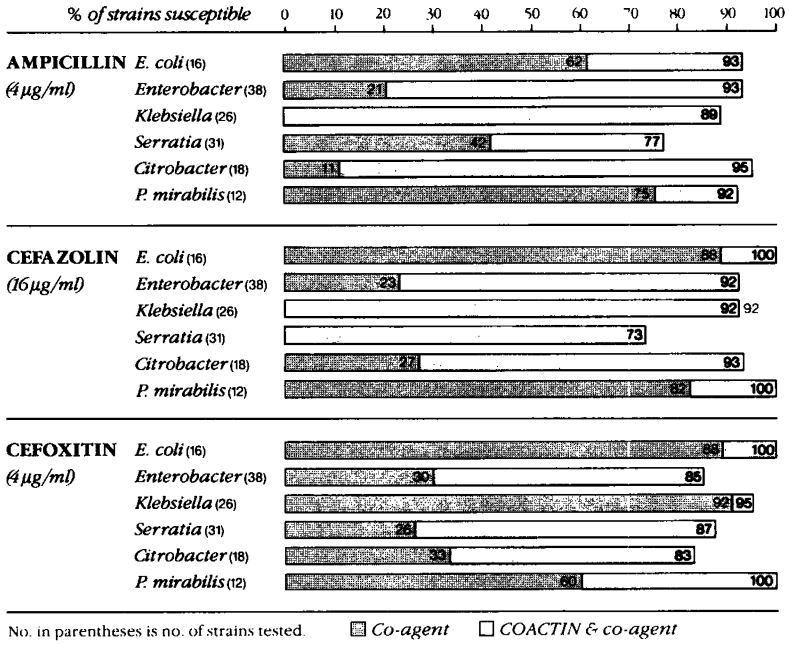
against gram-negative organisms.

In vitro: *Although a useful guide, in vitro activity does not necessarily correlate with clinical results.*

Enhanced activity in combination with penicillins and cephalosporins

Studies have shown that COACTIN (amdinocillin) enhances the activity of other beta-lactam co-agents that bind at complementary PBP-1 or PBP-3 sites.



No. in parentheses is no. of strains tested. ▨ *Co-agent* □ *COACTIN & co-agent*

The ratios of beta-lactam antibiotics to COACTIN in the combinations were based on those achieved in serum after parenteral administration of standard doses of the individual agents. The breakpoints for determining susceptibility to the co-agents were established based on these ratios and a 4 µg/ml breakpoint for COACTIN.

Combinations of COACTIN provide increased *in vitro* bactericidal activity against some strains with diminished susceptibility to the other beta-lactams.

Clinically:

Effective in combination in more serious urinary tract infections

COACTIN produced excellent results when used with beta-lactam co-agents for the treatment of uncomplicated and more serious complicated UTI, including pyelonephritis and pyelitis.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infections and determine their susceptibility to COACTIN or to its combination with another beta-lactam antibiotic.

Bacteriologic Cure*

Organism	*No. of Organisms*	*Eradicated No. (%)*
E. coli	39	39 (100.0)
P. mirabilis	4	4 (100.0)
Klebsiella- Enterobacter	20	19 (95.0)
S. marcescens	13	13 (100.0)
Other	6	5 (83.3)
Totals	**82**	**80 (97.6)**

*Data on file, Hoffmann-La Roche Inc.

Bacteremia associated with severe urinary tract infections due to *E. coli* has been successfully treated with COACTIN.

Adult dosage

COACTIN alone: 60 mg/kg/day given in divided doses (10 mg/kg every 4 hours). COACTIN in combination with another beta-lactam: 40 mg/kg/day given in divided doses (10 mg/kg every 6 hours). In patients with moderate to severe renal impairment (creatinine clearance less than 30 ml/min), the dosage should be limited to 10 mg/kg 3 or 4 times daily.

NEW **COACTIN®** IM IV *500-mg and 1-gm vials*
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Increase your chances for clinical success

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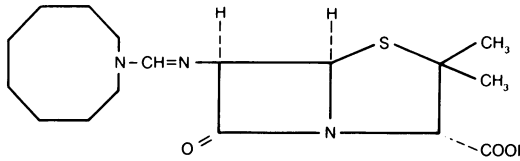
THE FIRST PBP-2 PENICILLIN

COACTIN® (amdinocillin)

DESCRIPTION: COACTIN® (amdinocillin) sterile is a semisynthetic penicillin for intramuscular or intravenous administration. Amdinocillin is a 6-β-amidinopenicillanic acid, different from other penicillins which are 6-β-aminopenicillanic acid derivatives. Chemically, amdinocillin is 6-β-[(hexahydro-1H-azepine-1-yl)-methyleneamino]-penicillanic acid, with an empirical formula of $C_{15}H_{23}N_3O_3S$.



Amdinocillin has a molecular weight of 325.43 and is supplied as a white to off-white crystalline powder which is readily soluble in water and methanol. The pKa values are 3.4 and 8.9 corresponding to an isoelectric point of 6.2. The pH of a 10% aqueous solution is 4.0 to 6.2. The reconstituted solutions are clear, almost colorless to yellow.

CLINICAL PHARMACOLOGY: Intravenous Administration: In healthy adult volunteers, mean plasma concentrations of amdinocillin following a 15-minute intravenous infusion of 10 mg/kg are shown below:

AMDINOCILLIN PLASMA CONCENTRATIONS (mcg/ml) IN ADULTS
I.V. Infusion

Dose	15 min	30 min	1 hr	2 hr	4 hr
10 mg/kg	61 (34-80)*	34 (26-43)	20 (13-25)	7.5 (6-10)	1.4 (0.7-1.9)

*Range

Following a 15-minute intravenous infusion of 10 mg/kg every 4 hours for a total of 6 doses in healthy adult volunteers, the mean steady state (after the second dose) maximum plasma concentrations ranged from 47 to 55 mcg/ml and the minimum steady state plasma concentrations ranged from 1.2 to 2.0 mcg/ml.

Intramuscular Administration: Amdinocillin is rapidly absorbed after intramuscular injection. Mean plasma concentrations following an intramuscular injection of 10 mg/kg in healthy adult volunteers are shown below:

AMDINOCILLIN PLASMA CONCENTRATIONS (mcg/ml) IN ADULTS
I.M. Injection

Dose	15 min	30 min	1 hr	2 hr	4 hr
10 mg/kg	18 (7-35)*	26 (14-44)	17 (10-29)	11 (5-22)	2 (0.8-5)

*Range

General: As with other penicillins, amdinocillin is excreted primarily by glomerular filtration and tubular secretion. In patients with normal renal function, approximately 70% of the administered dose is recovered in the urine within the first 6 hours after dosing. Following an intravenous infusion of 10 mg/kg, average concentrations of active drug in urine usually exceed 1000 mcg/ml within 30 minutes. At 4 to 6 hours after the infusion, average urinary concentrations usually decline to a range of about 97 to 135 mcg/ml. The average plasma elimination half-life of amdinocillin is approximately 51 minutes (range, 39 to 66 minutes) after intravenous administration; and 55 minutes (range, 39 to 64 minutes) after intramuscular administration. The rate of elimination is related to the degree of renal function impairment. In patients with severe renal insufficiency (creatinine clearance less than 10 ml/min), the mean half-life is slightly prolonged (3.3 hours). The drug is partially removed from the serum by hemodialysis and peritoneal dialysis. As with other penicillins, amdinocillin is metabolized only slightly. Following parenteral administration, the drug is present in active form in the serum, urine and bile, as well as in other body fluids and tissues. As with other penicillins, penetration into the cerebrospinal fluid (CSF) is generally poor; however, higher CSF concentrations are obtained in the presence of meningeal inflammation. Protein binding studies indicate that the degree of amdinocillin binding is low (5 to 10%).

Microbiology: Amdinocillin is highly active against gram-negative bacteria. It has low activity against gram-positive bacteria and is not active against *Pseudomonas* species, indole-positive *Proteus* species, anaerobic rods or enterococci.

Amdinocillin is usually active *in vitro* against strains of the following organisms, although clinical efficacy for infections other than those included in the Indications section has not been documented: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Citrobacter* species, *Shigella* species and *Salmonella* species.

Some strains of *Serratia* species are also susceptible.

Amdinocillin is more stable than ampicillin against β-lactamases, including the common plasmid-mediated TEM-1.

Unlike other penicillins that bind to penicillin-binding proteins $1B_S$ and 3, amdinocillin binds preferentially to penicillin-binding protein 2, causing the formation of spherical forms of bacteria by preventing cell elongation. This mechanism of action is primarily bacteriostatic; however, the high levels of amdinocillin achieved in the urinary tract provide bactericidal activity. *In vitro* studies have shown that amdinocillin acts synergistically in combination with other β-lactam antibiotics, enhancing their bactericidal activity against strains with diminished susceptibility. Susceptible strains include *E. coli*, *K. pneumoniae*, *Klebsiella* species, *Enterobacter* species, *S. marcescens*, *Serratia* species, *Proteus mirabilis* and *Citrobacter* species, as well as some strains of *Providencia* species, *Morganella morganii* and indole-positive *Proteus* species. To determine the synergistic activity of amdinocillin in combination with another β-lactam antibiotic against a particular microorganism, susceptibility testing should be performed.

Susceptibility Tests: Quantitative methods that require measurement of zone diameters give good estimates of bacterial susceptibility. One such procedure (Bauer AW, Kirby WM, Sherris JC, Turck M: Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol, 45:* 493-496, 1966; Standardized Disc Susceptibility Test, *Federal Register, 39:* 19182-19184, 1974) has been recommended for use with discs to test susceptibility to antimicrobials.

With this procedure, a report from the laboratory of "Susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "Resistant" indicates that the infecting organism may not respond to therapy and other therapy should be selected.

When the causative organism is tested by the Kirby-Bauer method of disc susceptibility testing, a 10-mcg amdinocillin disc should give a zone of 16 mm or greater to indicate susceptibility. Zone sizes of 15 mm or less indicate resistance.

Standardized procedures require use of control organisms. The 10-mcg amdinocillin disc should give zone diameters between 23 and 29 mm for the reference strain *E. coli* ATCC 25922.

Under certain conditions, it may be desirable to do additional susceptibility testing by broth or agar dilution techniques. An MIC of ≤4 mcg/ml can be considered susceptible. *E. coli* ATCC 25922 is the recommended reference strain for controlling amdinocillin dilution tests. Greater than 95% of MIC's for this control organism should fall within the range of 0.125 to 0.5 mcg/ml.

Suggested methods for susceptibility testing of amdinocillin in combination with other β-lactams: The macro-broth disc method is a simple test that can be employed to qualitatively determine the susceptibility of organisms to a combination of amdinocillin and another β-lactam antibiotic. In this test, an amdinocillin disc (10 mcg) and a standard disc of the other β-lactam antibiotic are added to 2 ml of Mueller-Hinton broth. The tube and a control tube are inoculated with 10 µl of a bacterial suspension prepared as described for the Kirby-Bauer disc test. The tubes are incubated overnight at 37°C. Inhibition of growth is considered to indicate susceptibility. This test is applicable to all organisms tested by the Kirby-Bauer method.

Broth dilution tests can also be carried out to quantitatively determine the susceptibility of organisms to amdinocillin in combination with other β-lactam antibiotics. MIC's are determined by testing the combined agents in ratios based on the mean serum levels achieved after parenteral administration of a standard dose of the individual agents. Organisms are considered susceptible if the MIC of each antibiotic in the combination falls within the range of susceptibility indicated for the individual components.

INDICATIONS AND USAGE: COACTIN® is indicated for the treatment of *complicated* and *uncomplicated urinary tract infections* caused by susceptible strains of *E. coli*, *Klebsiella pneumoniae*, *Klebsiella* species and *Enterobacter* species.

Bacteremia associated with severe urinary tract infection due to *E. coli* has been successfully treated with COACTIN.®

It has been demonstrated that amdinocillin acts synergistically with other β-lactam antibiotics. Therefore, combination therapy with various other β-lactam antibiotics may be considered in the treatment of more severe urinary tract infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infections and determine their susceptibility to amdinocillin or to its combination with another β-lactam antibiotic. Therapy with COACTIN® may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued. In certain severe infections when the causative organisms are unknown, COACTIN® may be administered with another appropriate β-lactam antibiotic as initial therapy. As soon as results of culture and susceptibility tests become available, antimicrobial therapy should be adjusted if indicated. Culture and susceptibility testing, performed periodically during therapy, will provide information on the therapeutic effect of the antimicrobial and will monitor for the possible emergence of bacterial resistance.

CONTRAINDICATIONS: COACTIN® is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have occurred in patients receiving a penicillin. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity reactions experiencing severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with amdinocillin is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to penicillins, cephalosporins or other drugs. Antibiotics should be used with caution in any patient who has demonstrated some form of allergy, particularly to drugs.

If an allergic reaction occurs during therapy with amdinocillin, the drug should be discontinued. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN AND INTRAVENOUS STEROIDS. AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE PROVIDED AS INDICATED.

PRECAUTIONS: General: Although COACTIN® shares with other penicillins the low potential for toxicity, as with any potent drug, periodic assessment of organ system functions, including renal, hepatic and hematopoietic, is advisable during prolonged therapy.

As with other antibiotics, prolonged use of COACTIN® may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate measures should be taken.

Drug Interactions: Probenecid interferes with the renal tubular secretion of amdinocillin, thereby increasing serum concentrations and prolonging the serum half-life of the antibiotic.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Considering the maximum duration of treatment and the class of the compound, carcinogenicity or mutagenicity studies with amdinocillin in animals have not been performed. The maximum durations of animal toxicity studies were 3 months parenterally and 6 months orally.

Amdinocillin produced no impairment of fertility in rats at daily doses up to 450 mg/kg, 7.5 times the recommended human dose.

Pregnancy: Pregnancy Category B. Reproduction studies have been performed in rats and mice at doses up to 7.5 times the recommended human dose and have revealed no evidence of harm to the fetus due to COACTIN.® There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Amdinocillin crosses the placenta and is found in low concentrations in cord blood and amniotic fluid.

Nursing Mothers: In limited studies, amdinocillin, following a single dose, has not been detected in the milk of nursing mothers; however, caution should be exercised when COACTIN® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions to COACTIN® which occur in about 5% of the patients are: *Hemic and lymphatic systems*: Eosinophilia and thrombocytosis. *Hepatic function tests*: Elevations of serum aspartate aminotransferase (SGOT) and serum alkaline phosphatase.

Less frequent adverse reactions, which occur in about 1% of the patients, are: *Hypersensitivity*: Rash. *Local reactions*: Thrombophlebitis. *Gastrointestinal*: Diarrhea and nausea. *Central nervous system*: Dizziness. *Hemic and lymphatic systems*: Anemia, neutropenia and leukopenia.

Other adverse reactions, which occur rarely (in less than 1% of the patients), are itching and/or urticaria, tenderness and/or pain at the injection site, vomiting, drowsiness or lethargy, elevated blood pressure, vaginitis, thrombocytopenia, and elevations of serum alanine aminotransferase (SGPT) or serum bilirubin.

OVERDOSAGE: There has been no experience to date with either deliberate or inadvertent overdoses of amdinocillin. As with other penicillins, COACTIN® in overdosage has the potential to cause neuromuscular hypersensitivity or convulsive seizures. Hemodialysis, if necessary, will aid in removal of the drug from the blood.

DOSAGE AND ADMINISTRATION: COACTIN® may be administered intravenously or intramuscularly. For serious infections, the intravenous route of administration is recommended. The recommended adult dosage for serious infections when COACTIN® is used alone is 60 mg/kg/day, given in divided doses (10 mg/kg every 4 hours). If the drug is to be given in combination with another β-lactam antibiotic, the daily dose of COACTIN® should be reduced to 40 mg/kg in divided doses (10 mg/kg every 6 hours).

Dosage for any individual patient must take into consideration the severity of infection, the susceptibility of the organisms causing the infection, and the status of the patient's host defense mechanism. The duration of therapy depends on the severity of infection. Generally, COACTIN® should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 10 days, but in complicated infections, more prolonged therapy may be required. In patients with moderate to severe renal impairment (creatinine clearance less than 30 ml/min), the dosage should be limited to 10 mg/kg 3 or 4 times daily.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The normal color of COACTIN® solutions is off-white to yellow.

DIRECTIONS FOR USE: Intravenous Administration: COACTIN® is administered intravenously by intermittent infusion. Reconstitute powder with Sterile Water for Injection, U.S.P.

Add the required amount of diluent to the drug powder in the vial; shake well and withdraw the entire contents. Further dilute, using aseptic technique, to 50 ml with 5% Dextrose Injection, U.S.P., and infuse the appropriate dose over 15 to 30 minutes. Other appropriate intravenous solutions at concentrations between 5 mg/ml and 100 mg/ml may be used (see Compatibility and Stability section).

Vial Size	Amount of Diluent to be Added	Concentration after Dilution to 50 ml
500 mg	4.8 ml	10 mg/ml
1 gm	9.6 ml	20 mg/ml

The solution of reconstituted drug may be administered by direct infusion or through a Y-type intravenous infusion set which may already be in place. If this method or the "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of COACTIN.®

When COACTIN® is given in combination with another antimicrobial, each drug should be given separately (not mixed physically) in accordance with the recommended dosages and routes of administration for each drug.

Intramuscular Administration: For intramuscular administration, use Sterile Water for Injection, U.S.P., or 0.9% Sodium Chloride Injection, U.S.P., for reconstitution.

Vial Size	Amount of Diluent to be Added
500 mg	2.2 ml
1 gm	4.4 ml

Dissolve drug powder in required volume of diluent and shake well. After reconstitution, each milliliter of solution will contain approximately 200 mg of amdinocillin. As with all intramuscular preparations, COACTIN® should be injected well within the body of a relatively large muscle, such as the upper outer quadrant of the buttocks (*i.e.*, gluteus maximus); aspiration will help avoid unintentional injection into a blood vessel.

COMPATIBILITY AND STABILITY: COACTIN® *intramuscular* solutions (1 gm/4.4 ml) remain stable (loss of potency less than 10%) for 16 hours when stored at room temperature or for 24 hours under refrigerated (5°C) storage condition.

COACTIN® *intravenous* solutions, at concentrations between 5 mg/ml and 100 mg/ml remain stable (loss of potency less than 10%) for the following time periods:

Diluent	Storage: Room Temperature	Storage: Refrigerated (5°C)
5% Dextrose*	24 hours	3 days
10% Dextrose*	24 hours	3 days
5% Dextrose + 0.45% Sodium Chloride*	24 hours	3 days
5% Dextrose + 0.9% Sodium Chloride†	24 hours	3 days
5% Dextrose in Ringer's†	24 hours	7 days
Lactated Ringer's with 5% Dextrose†	24 hours	7 days
Lactated Ringer's†	24 hours	7 days
Ringer's Injection*	24 hours	3 days
Sodium Lactate*	24 hours	3 days
0.9% Sodium Chloride	24 hours	7 days
0.45% Sodium Chloride†	24 hours	7 days
Sterile Water*	24 hours	3 days
10% Travert*	24 hours	3 days
5% Dextrose + Electrolyte #48	24 hours	3 days
5% Dextrose + Electrolyte #75	24 hours	7 days

*These solutions remain stable for 7 days under refrigerated conditions at 30 mg/ml or lower concentrations.
†These solutions remain stable for 14 days under refrigerated conditions at 30 mg/ml or lower concentrations.
Unused portions of solutions should be discarded after the time periods stated above.
The above stabilities apply to solutions stored in either glass or Viaflex (PVC) containers.

HOW SUPPLIED: Vials containing 500 mg equivalent of amdinocillin as a crystalline powder for reconstitution. Boxes of 10 (NDC 0004-1960-01).

Vials containing 1 gm equivalent of amdinocillin as a crystalline powder for reconstitution. Boxes of 10 (NDC 0004-1961-01).

COACTIN® vials should be stored at controlled room temperatures (59°F to 86°F).

THIS PRODUCT INFORMATION ISSUED FEBRUARY 1985.

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CUMITECH 20

Therapeutic Drug Monitoring: Antimicrobial Agents

by Stephen C. Edberg, Arthur L. Barry, and Lowell S. Young
Coordinating Editor: Josephine A. Morello

October 1984

This *Cumitech* reviews the clinical rationale for performing assays of antimicrobial agents and describes a number of microbiological, chromatographic, radioenzymatic, and immunological methods.

Therapeutic drug monitoring is warranted in a number of clinical situations:

- patients with serious infections who are treated with drugs having a narrow range between therapeutic and toxic levels (e.g., aminoglycosides), and in whom the relationship between dose and blood level of drug may be unpredictable, should be monitored frequently;
- chloramphenicol therapy can lead to dose-dependent depression of hematopoiesis unless drugs are monitored to prevent overdosing;
- drug assays are needed when extremely large doses of antimicrobial agents are used and shock, renal compromise, or both supervene;
- in certain life-threatening conditions, levels of antimicrobial agents may be monitored in body fluids other than serum.

Concise and clearly written, this *Cumitech* will be helpful in hospital laboratories, physicians' offices, and clinical microbiology laboratories.

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